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The Models Underlying the Anaesthesia Simulator Sophus

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ABSTRACT

This text describes the anaesthesia simulator Sophus developed in 1993 in cooperation between Herlev University Hospital, Risø National Laboratory and Roskilde University Center.

The simulator is based on several mathematical models treating different parts of the human physiology. Each model is described in a self contained way and may thus be studied separately. The interaction among all models in the simulator is described in detail, the implementation is documented and hints as to how future research could be undertaken is given. Finally, examples of the use of the simulator is given in the form of scenarios.

Preface

This report is a description of the models underlying the anaesthesia simulator Sophus. It serves as documentation of the models as well as the implementation developed in various meetings of the project participants from Herlev University Hospital, Roskilde University Centre and Risø National Laboratory.

We have benefited from the assistance of colleagues at their respective institutions. We especially wish to thank Viggo Andreasen, Johnny Ottesen, Melanie Stein, and Ole Møller Nielsen (Roskilde University Centre), Helle Ørding, Jesper Bo Hansen, and Tommy Christensen (Herlev University Hospital), and Jesper Larsen (Math-Tech).

The people participating in this project have quite diverse backgrounds; we have therefore striven to use a language almost understandable to all. However, we could not avoid using some terms specific to mathematics, medicine and computer science. Explanations of these terms may be found in standard textbooks.

Roskilde University, August, 1994

Mette Olufsen,
Finn Nielsen,
Per Føge Jensen,
Stig Andur Pedersen.

Contents

Chapter 1

Introduction

The Sophus group was founded in 1991 by Risø National Laboratory, Herlev University Hospital and Roskilde University Centre. The project has the following principle objectives:

- Development of a full-scale anaesthesia simulator.
- Development of mathematical models of the physiological processes in the human body and their behavior under influence of anaesthesia.
- Investigation of the cognitive aspects of anaesthesists' performance during surgery.
- Initiation of studies of human errors made by anaesthesists.
- Comparative studies of the various consequences when different levels of monitoring during anaesthesia are applied.

The efforts of the project group have led to the development of a prototype full-scale anaesthesia simulator. This includes the implementation of the physiological models and a user interface with the instructor. The Sophus group is currently conducting field studies of anaesthesists' performance during both real as well as simulated surgery.

1.1 Motivation

The project is motivated by the studies of Cooper, et al. [1]. In these he estimated that 80 percent of preventable critical incidents inflicted by anaesthesia are due to human error; the remainder to equipment failure. Inexperience with equipment and shortage of trained staff were the factors most often identified as contributing to the incidents.

During the last decade decision making theory has been applied to clinical decision making. Gaba, et al. have in [2] implemented training programmes in which anaesthetists receive instruction in dynamic decision making and human performance issues in anaesthesia, and then undergo simulation sessions in a comprehensive anaesthesia-simulation environment.

We believe that hands-on training in management of critical incidents and an increased awareness of decision making theory and human performance issues should become a regular part of the initial and continuing education of anaesthesists. We believe that training in the diagnosis and treatment of critical events will enhance the ability of physicians to deal with critical incidents.

Furthermore, we hope that the development of the simulator will provide some new mathematical insight into the physiological models of the human organism.

1.2 Description of the simulator

1.2.1 Design

The anaesthesia simulator developed by Herlev University Hospital, Roskilde University and Risø National Laboratory is a near-replica of the anaesthetic work environment. The total simulation system consists of three major components: The simulation program PAWI 2.7, which runs on an IBM-compatible PC, the simulation Environment, and an instructor's Console.

1.2.2 The simulation program

All essential physiological parameters are animated and controlled by the computer. The simulation of human response to anaesthesia is based on mathematical models of pharmacokinetic and pharmacodynamic processes, the cardiovascular system and the respiratory system.

1.2.3 The simulation Environment

The anaesthesia-simulation environment, including a mannequin, can be connected to commonly used anaesthesia machines and monitoring equipment, and the simulations can therefore take place in a real operating theater. The mannequin can be intubated, and it simulates human metabolism through "production" of CO_2. This allows the use of capnographs, mass spectrometers and other monitors commonly used for monitoring exhaled gases. ECG's (including arrhythmia and ischaemia), pulse oxymetry, invasive pressures (3 channels), temperature and non-invasive blood pressure are transmitted from the workstation to the monitoring equipment.

1.2.4 The Instructor's Console

This component provides both monitoring and controlling functions for the instructor. Scenarios are carried out through the use of scripts containing a number of events scheduled at different times. During a simulation the instructor may introduce events or disable planned events by overriding the script. Training scenarios include sessions with cardiac arrest, malignant hyperthermia, disconnects, pneumothorax, etc.

This report is primarily concerned with the description of the components that make up the simulation program. Furthermore, it briefly describes the use of the simulation-program.

The chapters 2 – 6 describe the individual components of the compound model. Chapter 7 provides an overview of the connections among these components, including input and output specifications as well as the inter-dependencies between model parameters. Chapter 9 provides an

example of the use of a simulation script in connection with a specific scenario.

Finally the model status is elaborated in chapter 10.

For a concrete user's guide to the program we refer the reader to the report [5].

Chapter 2

The ECG model

The ECG model draws on a database of piecewise linear functions, each representing an ECG for one heart cycle. During a simulation the program continuously generates the ECG by channeling the chosen piecewise linear function through a filter. The basic idea in this approach is taken from [12]. It is possible to choose among approximately twenty different functions corresponding to different arrhythmias. It is also possible to edit an existing piecewise linear function in order to create a new type of ECG. The latter can be done interactively.

The filter converting the piecewise linear function to a smooth ECG is a low-pass filter that can be described using electrical circuits consisting of the components shown in figure 2.1.

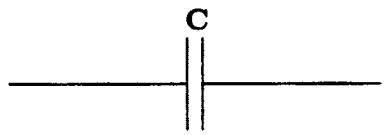
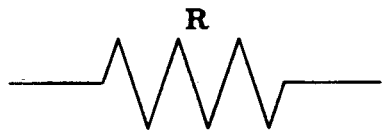
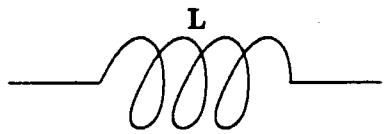
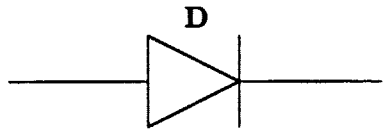
Symbol	Electrical component	Physiological property	Mathematical definition
	Capacitor	Compliance	$Q_C = C\frac{dP_C}{dt}$
	Resistor	Resistance	$P_R = RQ_R$
	Inductor	Inertia	$P_L = L\frac{dQ_L}{dt}$
	Diode	Valve	

Figure 2.1: The relevant electrical components and the corresponding meaning in fluid dynamics. In the first equation the flow Q is proportional to the compliance and the difference in pressure over the capacitor. In the second equation the pressure P is proportional to the resistance R and the flow through this. In the last equation the difference in pressure over the inductor is proportional to the inertia of the blood and the change of flow through the inductor.

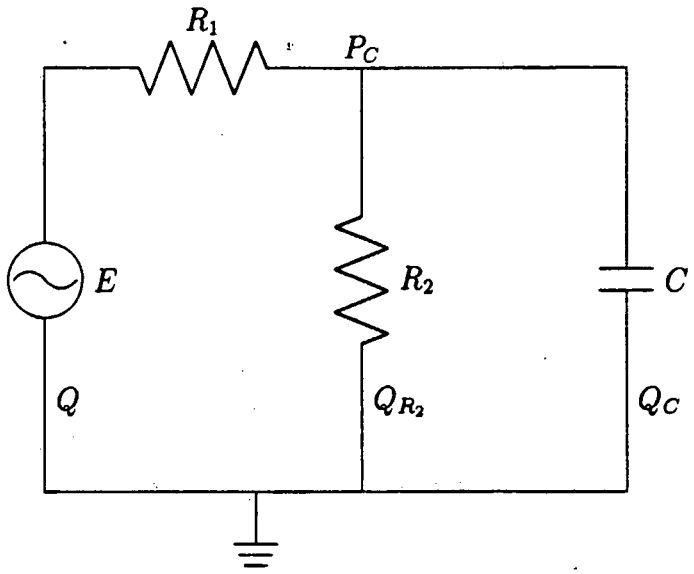


Figure 2.2: The circuit corresponding to the filter used for smoothing the piecewise linear ECG.

The ECG filter is based on the electrical circuit shown in figure 2.2 (cf. [12]). The purpose of the filter is to smooth the signal in order to avoid step changes in the resulting ECG.

In accordance with Kirchoff's current-law and by use of the definitions for the various electrical components (displayed in figure 2.1) it is possible to obtain the equations for the filter.

The total flow is given by

$$\begin{aligned} Q &= Q_{R_2} + Q_C \quad \Leftrightarrow \\ Q - Q_{R_2} &= C\frac{dP_C}{dt} \quad \Leftrightarrow \\ \frac{E - P_C}{R_1} - \frac{P_C}{R_2} &= C\frac{dP_C}{dt} \end{aligned}$$

where $E - P_C$ is the pressure difference over the resistance R_1. The input to the filter is a piecewise linear function (E) and the output (P_C) is a vector consisting of 60 equidistant numbers representing the electrical potential during one heart cycle. P_C is used as an input to the cardiovascular model, which in turn uses the pulse to create the output to the anaesthetic monitors.

This transformation is shown in figure 2.3.

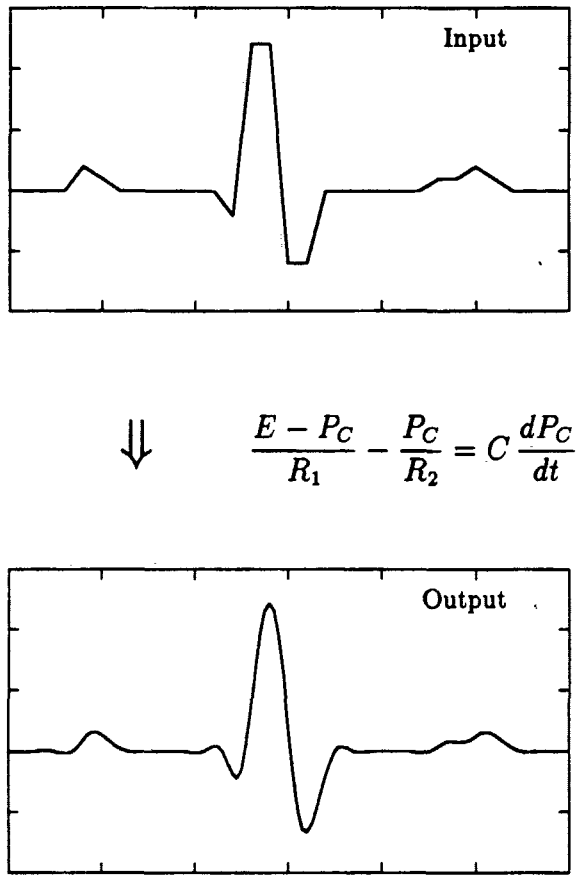


Figure 2.3: The transformation from a piecewise linear function to an ECG.

Chapter 3

The plethysmographic model

This model consists of two parts. The first, made up of two sine functions, creates the pleth and the second provides the strength of the pulse.

The sine functions used to create the actual curve for the pleth are defined as

$$p(t) = A \sin(0.7\omega t) \qquad \text{for } t \leq T_0 \tag{3.1}$$

$$p(t) = A\,0.8 \sin(0.5\omega t) \qquad \text{for } t > T_0 \tag{3.2}$$

where A is the amplitude of the pleth, ω is the cyclic frequency, and T_0 is half the period. The constants used in the equations are obtained by fitting the functions to a clinical recording of a normal plethysmograph curve.

The amplitude varies between 0 – 100 % and represents the pulse strength. This quantity can either be determined by the instructor during a simulation session or it can be predefined in a user script.

The frequency ω is defined as

$$\omega = \frac{2\pi}{T_P}$$

where $T_P = 2T_0$ is the time used in order to create one heartbeat.

The graph for one period is shown in figure 3.1.

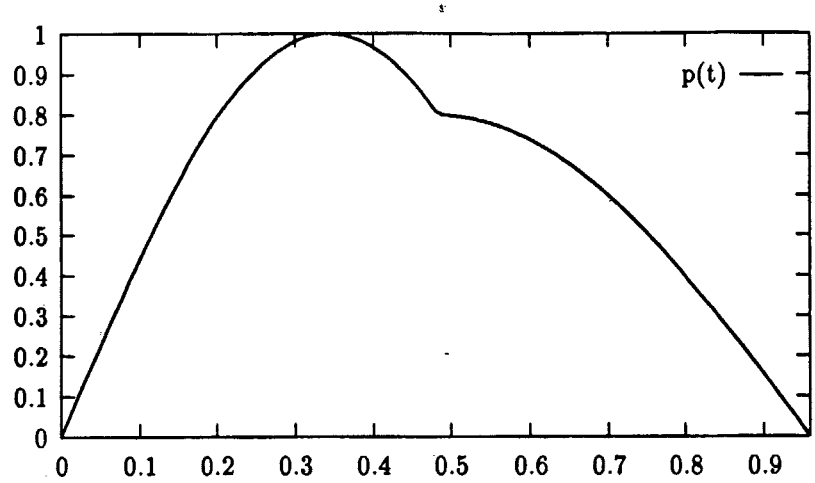


Figure 3.1: The plethysmographic curve is composed of two sine functions.

In addition to the amplitude A, the oxygen saturation of the blood is also displayed on the anaesthetic monitor. The value of this parameter is stated directly in the user scripts.

A more detailed documentation of the course of a simulation session is described in chapter 9.

Chapter 4

The pharmacokinetic and pharmacodynamic models

The pharmacokinetic and pharmacodynamic models are inherently two distinct models and we will treat them separately throughout this report. However, in the program there is no such distinction.

The pharmacokinetic model is itself composed of two models, one for inhalation agents and one for intravenous drugs. The outputs of both are given as the concentration of an agent in a given compartment of the body, and are then treated by the pharmacodynamic model, which converts the concentration to a physiological effect on the body.

4.1 The pharmacokinetic models

The model concerning **inhalation agents** is based on physiological compartments, using the ideas from [6]. The concentration of the inhalation anaesthetic isoflurane, enflurane and halothan are predicted in fourteen compartments of the body. However, the only concentration used in the simulator is that found in the brain, since this is sufficient as input to the pharmacodynamic model. Several versions of the fourteen-compartment model are described in [6]; We have implemented the version without a peripheral shunt (Lerou's version A).

The model concerning **intravenous drugs** is based on a hypothetical depiction of the human body consisting of a three-compartment model, as described by C.J. Hull in [3] and [4].

There are three groups of input data to each of the pharmacokinetic models: The first consists of anaesthetic agents, entered at the console by the instructor during a simulation. This is done in response to the actions performed by the trainees. The second input consists of the cardiac output values from the cardiovascular model. This information is updated every fourth heartbeat. Finally, the model uses various pieces of basic information such as the body weight, age, gender, etc. These are given in the set-up scripts.

The output is the concentration of the anaesthetic agent in question. In the case of the fourteen-compartment model the concentration is calculated for the brain compartment, and in the three-compartment model the concentration is calculated for a fictive effector compartment.

4.1.1 The fourteen-compartment model

The uptake and distribution of inhalation agents in the body and the anaesthetic circuit are simulated by a system of fourteen compartments. The anaesthetic agent is absorbed from the lung circuit compartment and is subsequently distributed to the other compartments; kidney, brain, heart, liver, muscle, connective tissue and adipose tissue. The model allows for the subject's age, body weight, height and other physiological variables. The data for total blood volume, cardiac output, tissue volumes, tissue blood flows and partition coefficients are due to the work of Lowe and Ernst [7].

The model is based on the following assumptions:

1. All blood is regarded as stored in pools (Mapleson's concept [8]), thus simulating the differences in circulation times that exist in the body.

2. The only exchange of anaesthetic agents between compartments is via the anaesthetic circuit or the blood.

3. Equilibrium within a compartment is instantaneous.

4. The agents are not metabolized.

Each compartment is characterized by its solubility, volume and blood flow. It is assumed that the volume of each compartment is constant.

The most important parameter is the cardiac output, since this determines the blood flow through the tissues and therefore also the amount

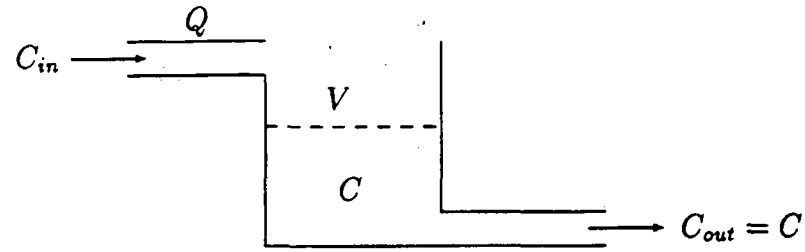


Figure 4.1: A generic compartment. The speed of the inflow equals that of the outflow and the concentration in the outflow equals the concentration in the compartment.

of anaesthetic passed through the respective compartments. The cardiac output is obtained from the cardiovascular model. The change of drug concentration in each compartment can be expressed as a simple first-order ordinary differential equation. This is derived for a generic compartment (see figure 4.1) involving the following variables:

C_{in}: Concentration of anaesthetic in the blood entering the compartment.

C_{out}: Concentration of anaesthetic in the blood leaving the compartment. This is assumed to be equal to the concentration inside the compartment.

X: The absolute amount of anaesthetic in the compartment.

Q: Volume flow velocity through the compartment.

V: The volume of the compartment.

The total amount of anaesthetic in a generic compartment is thus given by:

$$X = C_{out} V$$

The change in the amount of anaesthetic can be calculated as the amount going in minus the amount going out during the interval dt:

$$dX_{in} - dX_{out} = (C_{in} - C_{out})\, Q\, dt$$

This leads to the following equation:

$$\begin{aligned} dX &= dX_{in} - dX_{out} = (C_{in} - C_{out})\, Q\, dt \\ \frac{dC_{out} V}{dt} &= (C_{in} - C_{out})\, Q \\ \frac{dC_{out}}{dt} &= \frac{(C_{in} - C_{out})\, Q}{V} \end{aligned}$$

Figure 4.2 shows the fourteen compartments.

Compartment 1 models the anaesthetic circuit. The lungs are modelled in compartment 2, while the vascular system is divided between compartment 3 and 14, which model the arterial and venous pool ventricles, respectively.

The viscera (kidney, brain, heart muscle and liver) are represented by the compartments 4 to 7, muscles and connective tissue in 8 and 9 while the adipose tissue is modelled in compartment 10.

The blood in the viscera is modelled separately in the compartments 11 to 14. Some of the blood may not enter any of the organs in question. This is modelled by the peripheral shunt.

The actual equations for the fourteen chambers are shown below.

Compartment 1: The equation governing the anaesthetic circuit

$$\frac{dC_C}{dt} = \frac{(C_A - C_C)\,Q_A + V_{an} - V_{leak}}{V_C + V_D}$$

where $V_{leak} = 0.05\,(C_C + C_A)$.

Compartment 2: The equation governing the lungs

$$\frac{dC_A}{dt} = \frac{(C_C - C_A)\,Q_A - (1 - f_s)\,(\lambda_b C_A - C_{v_o})\,Q}{V_L}$$

where $f_s = 0.05$ is the blood passing through the pulmonary shunt.

Compartment 3: The equations governing the arterial pool.

The concentration of gas from the lungs (C_{a_e}) is given by

$$C_{a_e} = \lambda_b\, C_A$$

where λ_b is the blood/gas coefficient.

The concentration of anaesthetic entering the arterial pool is partly due to the blood coming from the lungs C_{a_e} and partly due to unoxygenized blood entering through the pulmonary shunt.

$$C_{a_i} = C_{a_e}\,(1 - f_s) + C_{v_o} f_s$$

The change in the concentration is thus given by:

$$\frac{dC_{a_o}}{dt} = \frac{Q\,(C_{a_i} - C_{a_o})}{V_{ap}}$$

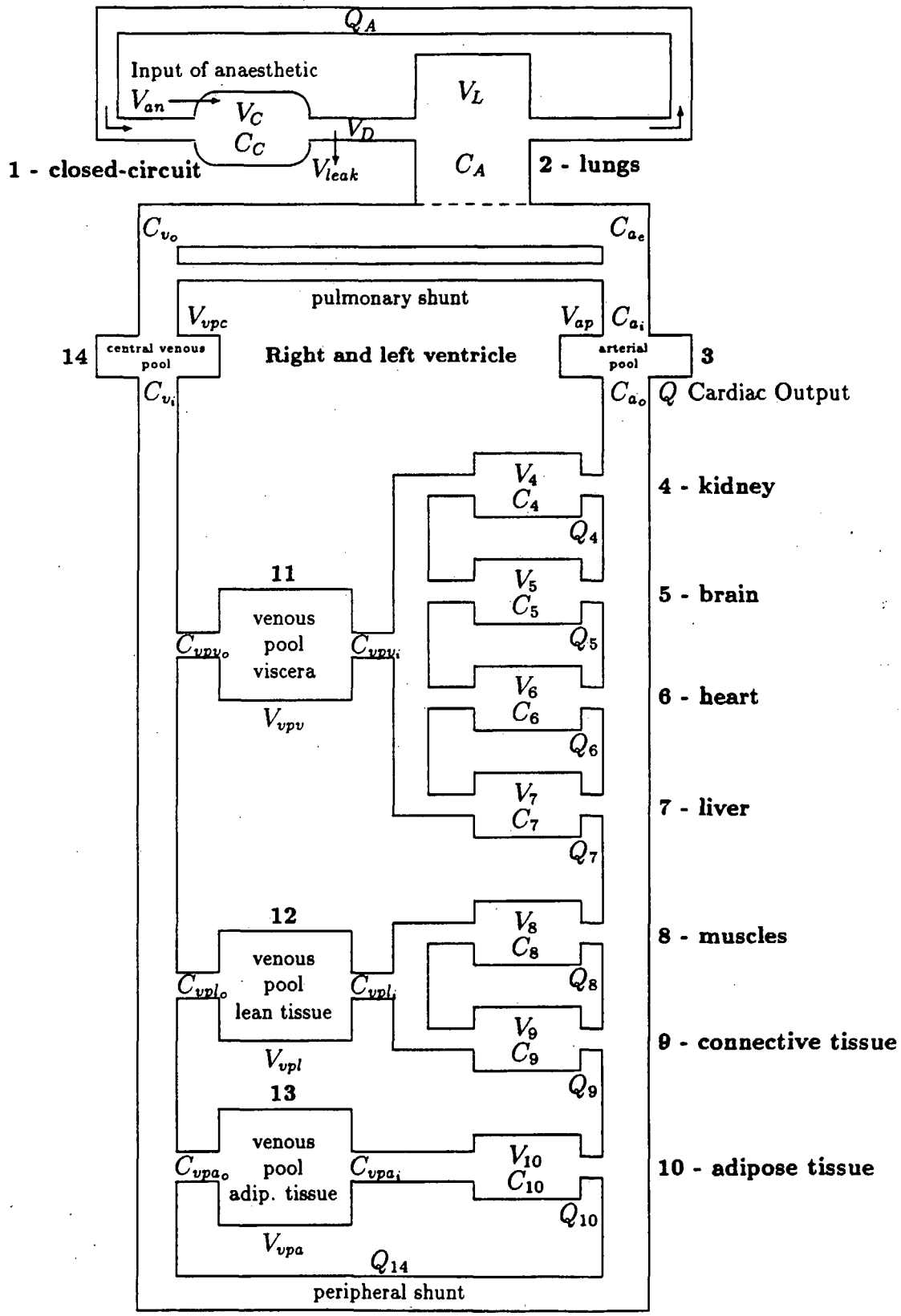


Figure 4.2: The fourteen-compartment model.

Compartment 4-10: The equations governing the viscera, muscles, connective and adipose tissue

$$\frac{dC_{w_i}}{dt} = \frac{Q_i\,(C_{a_o} - C_{w_i})}{V_i\,\lambda_i} \qquad \text{for i} = 4, 5, \ldots, 10$$

where λ_i is the tissue/blood coefficient.

Compartment 11: The equations governing the total blood volume of the viscera.

The concentration of anaesthetic in the blood entering the compartment is given by:

$$C_{vpv_i} = \frac{\sum_{i=4}^{7} C_i\,Q_i}{\sum_{i=4}^{7} Q_i}$$

This gives rise to the following change in the concentration:

$$\frac{dC_{vpv_o}}{dt} = \frac{(C_{vpv_i} - C_{vpv_o})\,\sum_{i=4}^{7} Q_i}{V_{vpv}}$$

Compartment 12: The equations governing the total amount of blood in muscles and connective tissue.

The concentration of anaesthetic in the blood entering the compartment is given by

$$C_{vpl_i} = \frac{\sum_{i=8}^{9} C_i\,Q_i}{\sum_{i=8}^{9} Q_i}$$

which gives rise to the following equation for the change in the concentration:

$$\frac{dC_{vpl_o}}{dt} = \frac{(C_{vpl_i} - C_{vpl_o})\,\sum_{i=8}^{9} Q_i}{V_{vpl}}$$

Compartment 13: The equations governing the adipose tissue.

Since only one organ is present in this case, the concentration of anaesthetic in the entering blood will equal the concentration in the adipose tissue.

$$C_{vpa_i} = C_{10}$$

The change in the concentration is therefore given by:

$$\frac{dC_{vpa_o}}{dt} = \frac{Q_{10}(C_{vpa_i} - C_{vpa_o})}{V_{vpa}}$$

Compartment 14: The equations governing the blood entering the venous pool.

The concentration of anaesthetic in the blood from the various viscera and the peripheral shunt is given by

$$C_{v_i} = C_{vpv_o}\frac{\sum_{i=4}^{7} Q_i}{Q} + C_{vpl_o}\frac{\sum_{i=8}^{9} Q_i}{Q} + C_{vpa_o}\frac{Q_{10}}{Q} + C_{a_o}\frac{Q_{14}}{Q}$$

which gives

$$\frac{dC_{v_o}}{dt} = \frac{Q(C_{v_i} - C_{v_o})}{V_{vpc}}$$

In our implementation the pharmacodynamic model only uses the brain concentration (C_5) even though all concentrations are calculated.

The actual parameters used in this model are defined in appendix A.

4.1.2 The three-compartment model

This model predicts the concentration of intravenous drugs in the blood plasma by use of a three-compartment model. The concept of the three-compartment model is elaborated by C.J. Hull in [3] and [4].

It should be noted that the three compartments are fictive in the sense that they do not have direct physiological equivalents as do the compartments in the previous model. Rather, they represent different aspects of the drug elimination process.

The basic idea is to obtain a model by fitting a curve to the decay of various drugs in the body. For most agents this can be done using a linear combination of three exponential functions.

The three-compartment model is illustrated in figure 4.3.

Determination of the constants

C. J. Hull considers a system of three compartments of fictive volumes in order to reflect different rates of decay.

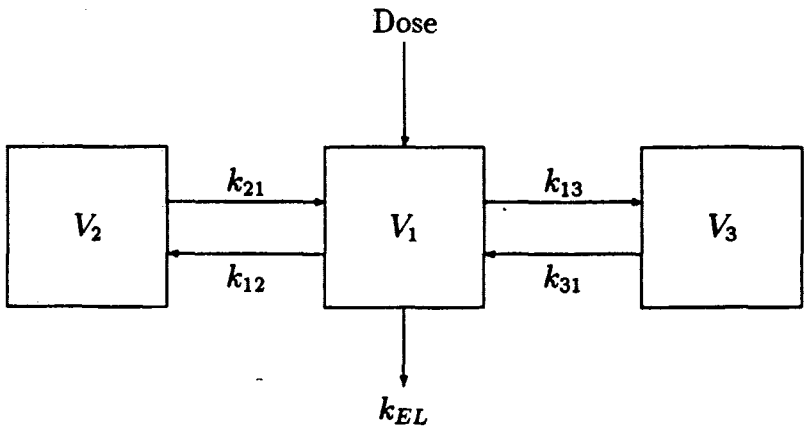


Figure 4.3: The three-compartment model.

For compartment n define the following:

$X_n(t)$	is the mass of drug as a function of time.
V_n	is the volume of the compartment. It is fictive in the sense that it is calculated as $V_n = X_n(0)/C_n(0)$, where $X_n(0)$ is the injected dose and $C_n(0)$ is the concentration measured immediately after injection.
$C_n(t)$	is the concentration of drug. It varies in time, and is given by $C_n(t) = X_n(t)/V_n$.

Finally, let k_{ij} be the rate of flow from compartment i to compartment j.

In figure 4.3 a dose ($X_n(0)$) is injected into compartment 1 from which the drug is eliminated with the rate k_{EL}. In addition, the drug is exchanged with the compartments 2 and 3. The change of mass in each compartment may therefore be described as the system $\mathbf{A}X = \frac{dX}{dt}$ of first order differential equations:

$$\begin{pmatrix} -(k_{12}+k_{13}+k_{EL}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix} = \begin{pmatrix} \frac{dX_1}{dt} \\ \frac{dX_2}{dt} \\ \frac{dX_3}{dt} \end{pmatrix} \quad (4.1)$$

Assuming that the matrix $\mathbf{A}$ has three distinct real eigenvalues, the

solution to (4.1) has the following form:

$$\begin{pmatrix} a & b & c \\ p & q & r \\ l & m & n \end{pmatrix} \begin{pmatrix} e^{-\lambda_1 t} \\ e^{-\lambda_2 t} \\ e^{-\lambda_3 t} \end{pmatrix} = \begin{pmatrix} C_1 \\ C_2 \\ C_3 \end{pmatrix} \tag{4.2}$$

where $C_n(t) = X_n(t)/V_n$.

The eigenvalues λ_1, λ_2 and λ_3 can be found as the roots of the characteristic polynomial corresponding to the linear system given in equation (4.1).

The characteristic equation $\det(\mathbf{A} - \lambda\mathbf{I}) = 0$ is given by:

$$\begin{aligned}(k_{12} + k_{13} + k_{EL} + \lambda)(k_{21} + \lambda)(k_{31} + \lambda) + \\ k_{21}k_{12}(k_{31} + \lambda) + k_{31}k_{13}(k_{21} + \lambda) &= 0\end{aligned}$$

which after reordering is

$$\begin{aligned}-\lambda^3 - (k_{31} + k_{21} + k_{12} + k_{13} + k_{EL})\lambda^2 - \\ (k_{21}k_{31} + k_{12}k_{31} + k_{13}k_{21} + k_{EL}k_{31} + k_{EL}k_{21})\lambda - \\ (k_{21}k_{31}k_{EL}) &= 0\end{aligned}$$

in which we assume $(\lambda_1, \lambda_2, \lambda_3) \in \mathbb{R}^3$.

The remaining constants in equation (4.2) are given as a consequence of the initial conditions for $X_i(0)$ for $i := 1, 2, 3$:

$$\begin{aligned}
a &= \frac{C_1(0)({\lambda_1}^2 - (k_{21} + k_{31})\lambda_1 + k_{21}k_{31})}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_1)} \\
b &= \frac{C_1(0)({\lambda_2}^2 - (k_{21} + k_{31})\lambda_2 + k_{21}k_{31})}{(\lambda_3 - \lambda_2)(\lambda_2 - \lambda_1)} \\
c &= \frac{C_1(0)({\lambda_3}^2 - (k_{21} + k_{31})\lambda_3 + k_{21}k_{31})}{(\lambda_3 - \lambda_2)(\lambda_1 - \lambda_3)} \\
m &= \frac{C_1(0)k_{31}(k_{21} - \lambda_2)}{(\lambda_3 - \lambda_2)(\lambda_2 - \lambda_1)} \\
n &= \frac{C_1(0)k_{31}(k_{21} - \lambda_3)}{(\lambda_3 - \lambda_2)(\lambda_1 - \lambda_3)} \\
l &= -(m + n) \\
q &= \frac{C_1(0)k_{21}(k_{31} - \lambda_2)}{(\lambda_3 - \lambda_2)(\lambda_2 - \lambda_1)} \\
r &= \frac{C_1(0)k_{21}(k_{31} - \lambda_3)}{(\lambda_3 - \lambda_2)(\lambda_1 - \lambda_3)} \\
p &= -(q + r)
\end{aligned}$$

The concentration in the blood plasma (C_1) can now be predicted for any value of t using the constants a, b and c.

4.2 The pharmacodynamic model

The output from the two pharmacokinetic models are passed as input to the pharmacodynamic model. In this model the concentration of anaesthetic in the body is converted to a physiological effect using the Hill equation (cf. [16]). This approach is based on the concept that the pharmacodynamic effect depends on the number of receptors occupied by the drug. This effect is subsequently transferred to both the Cardiovascular and the Baroreceptor models.

The Hill equation is given by

$$E = \frac{C^\gamma}{C^\gamma + Ce_{50}^\gamma} \text{MaxE} \tag{4.3}$$

where E is the intensity of the effect and C is the concentration of anaesthetic in the brain and in the blood plasma, for the fourteen-compartment model and the three-compartment model, respectively. Ce_{50} is a constant defined as the resulting value of the compartment concentration that alters from administration of an Ed_{50} dose. Ed_{50} is thus the dose required to give half of the full effect. MaxE is a constant representing the maximal effect of the anaesthetic agent in question. Finally γ is a parameter that allows the sigmoidicity of C to affect the relationship. Besides the effect obtained by MaxE, the drug can have additional class effects. These can be classified as follows ([14, page 17]):

Class	Drugs in class
BenzA	Midazolam, diazepam, flumazenil
BenzB	Midazolam, flumazenil
Alpha	Alpha agonists and antagonists
Beta	Beta-1 agonists and antagonists

In our simulator these classes are renamed respectively as: ClassA, ClassB, α- and β-agonist.

The parameters of the cardiovascular model are determined according to the formulas, that follow.

4.2.1 Updating of the heart rate

For $\gamma = 2$ ([16]), the Hill equation gives

$$HR := HR + \text{MaxE}\frac{C^2}{C^2 + Ce_{50}^2} \tag{4.4}$$

where MaxE depends on the drug. If the maximal heart rate (MaxHr) is greater than zero then MaxE := MaxHr. However, if the drug has an additional classB effect, the heart rate is further modified by using (4.4) again. If the drug is α-agonist, MaxE is assigned the value of the maximum heart rate; otherwise the minimum heart rate is used.

4.2.2 Updating of the maximal elastance (E_{max}) of the systemic and pulmonary circuits

The equation used to modify the maximum elastance of the systemic circuit is given below. Updating the maximum elastance of the pulmonary circuit is done analogously by replacing E_{max_l} with E_{max_r}:

$$E_{max_l} := E_{max_l} + \text{MaxE}\frac{C^2}{C^2 + Ce_{50}^2}$$

These modifications follows exactly the same pattern as the heart rate modification.

4.2.3 Updating of the systemic and pulmonary vascular resistances

Only the equation governing the systemic resistance is presented:

$$R_{svs} := R_{svs} + \text{MaxE}\frac{C^2}{C^2 + Ce_{50}^2}$$

The same pattern as before is followed, but in this case the resistance is further modified if the drug belongs to classA.

The parameter (K_x) concerning the effect of the baroreceptor is changed analogously:

$$K_x := 1 - \text{MaxE}\frac{C^2}{C^2 + Ce_{50}^2}$$

This is done only if the maximal baroreceptor effect is positive, i.e. if $K_x > 0$, otherwise there is no further updating.

Chapter 5

The cardiovascular model

The cardiovascular model is based on the Windkessel approximation and the development is primarily based on [15] and [13]. The model is extended by adding the components representing the right arm and the pulmonary system in order to model the central haemodynamics.

The most important output from the cardiovascular model is the cardiac output ($Q_A = CO$) and pressures in the aorta, pulmonary artery, and radial artery. The latter makes it possible to obtain values corresponding to the non-invasive blood pressure. Furthermore, the value for the cardiac output is transferred to the pharmacokinetic model.

The original model is represented by analog electrical circuits, and the equations are constructed from the fundamental laws of resistance, compliance and inertia. In addition, the aortic and pulmonary valves, which are non-linear elements, are modelled using two equations; one when the valves are open and another when they are closed.

This model is based on the relationships described on page 6 in chapter 2.

The definition of the elastance E by Sagawa and Sunagawa has been applied:

$$P(t) = E(t)\,(V - V_D) \tag{5.1}$$

where V_D is the dead space volume of either the left (V_{DLV}) or the right (V_{DRV}) ventricle. This does not contribute to the pressure generation during the systole. Finally $E(t) = 1/C$ is the elastance of the heart. The elastance concept is further elaborated in section 5.2.

We will derive the equations governing the systemic circuit in section 5.1. The equations for the pulmonary circuit are derived analogously and will be described briefly in section 5.3. The initial values used as well as the values of the constants are given in appendix A.

5.1 The models concerning the systemic circuit

The functionality of the circuit in figure 5.1 can be described in seven equations.

5.1.1 Equation one – the left ventricle pressure

Using the definition of $E(t)$ given in (5.1), it is possible to calculate the pressure of the left ventricle by

$$P_{LV} = \frac{1}{C_{LV}} (V_{LV} - V_{DLV}) \tag{5.2}$$

where P_{LV}, C_{LV}, V_{LV} denote the pressure, compliance and volumes of the left ventricle, respectively, and V_{DLV} is the volume of the dead space of the left ventricle. Looking at the change of pressure with respect to time (i.e. differentiating (5.2) with respect to t). Assuming that the volume of the dead space is constant, it is possible to get the following expression for the flow Q_A through the aorta:

$$Q_A = -\frac{dV_{LV}}{dt} = -\frac{dC_{LV}}{dt} P_{LV} - C_{LV} \frac{dP_{LV}}{dt}$$

The cardiac output is determined at the beginning of the aorta, hence the subscript A. Thus the final equation for the cardiac output is given by:

$$C_{LV} \frac{dP_{LV}}{dt} = -Q_A - P_{LV} \frac{dC_{LV}}{dt} \tag{5.3}$$

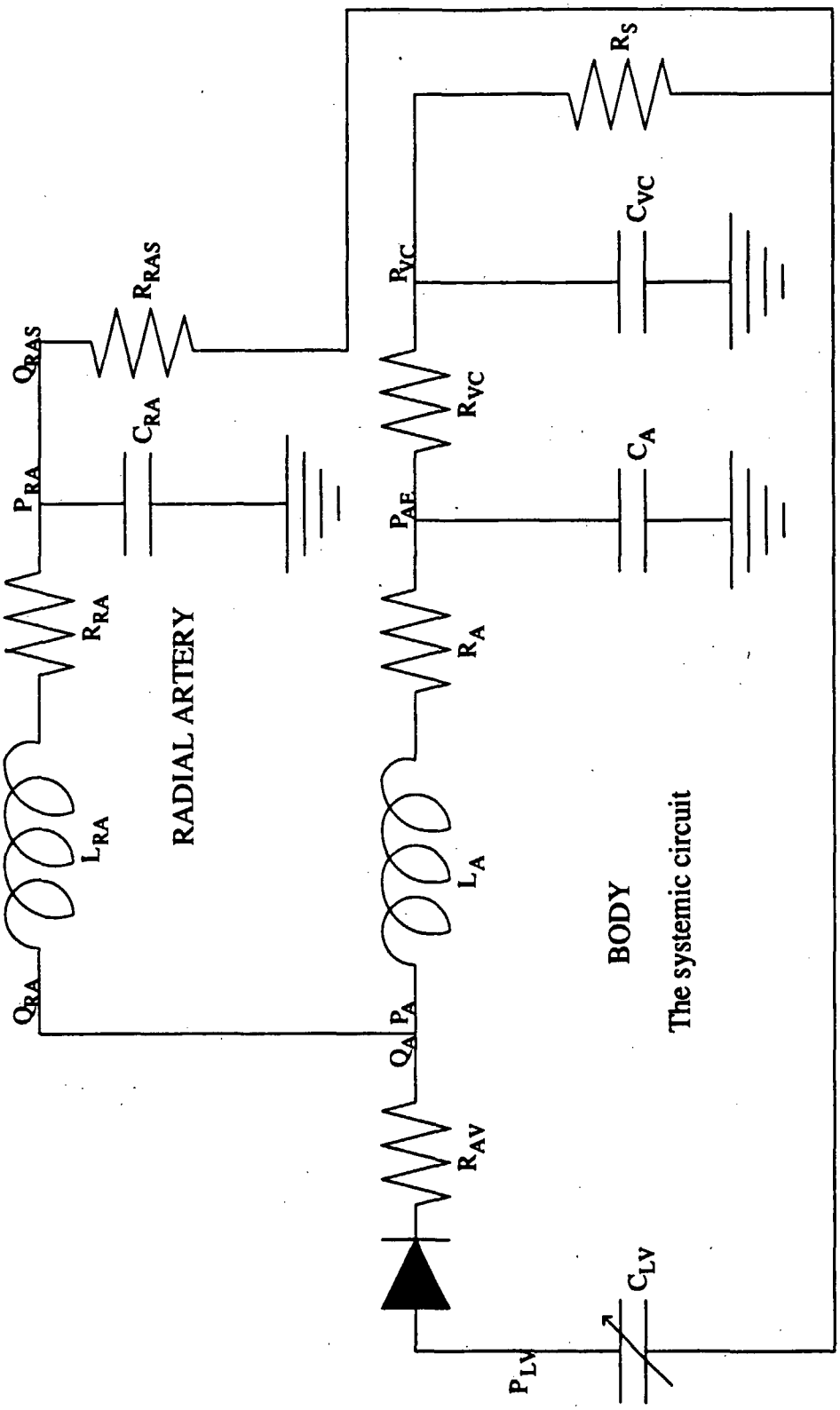


Figure 5.1: The systemic circuit.

5.1.2 Equation two – the aortic valve

The aortic valve is physiologically either open or closed, corresponding to the systole or the diastole, respectively. Therefore the aortic valve is represented by a diode in the electrical circuit. The valve is open as long as the pressure in the left ventricle P_{LV} is greater than the aortic pressure P_A, and it closes whenever the pressure in P_{LV} decreases below a certain point (the beginning of the diastole).

A way to describe the closed valve might be to raise the corresponding resistance R_{AV} dramatically, but this results in unwanted oscillations in the system. If instead the resistance is modelled by an exponential function, the system reacts more accurately, but the solutions are still not sufficiently stable. However, the latter approach has the advantage of being smooth, which makes it easier to calculate the derivatives numerically.

We have chosen to view the aortic valve as a discrete process, represented by two different equations corresponding to the two states. This gives the desired behavior and the solution to each of the equations is sufficiently stable.

The equation for the open valve is thus obtained by regarding the difference in pressure over the resistance in the left ventricle. According to Ohm's law we get

$$\begin{aligned} P_{LV} - P_A &= R_{AV}\, Q_A \qquad \Leftrightarrow \\ \frac{dP_A}{dt} &= \frac{dP_{LV}}{dt} - R_{AV}\frac{dQ_A}{dt} \end{aligned} \tag{5.4}$$

where P_A is the aortic pressure and R_{AV} the resistance of the aortic valve which is constant. Since the valve is open we have $Q_A > 0$.

When the valve closes, the flow Q_A disappears and the change of pressure at the beginning and end of the aorta will consequently become the same. This equality leads to the following expression for $Q_A \leq 0$

$$P_A = P_{AE} \tag{5.5}$$

where the subscript AE refers to the end of the aorta. The initial condition for this equation is the value of P_{AE} at time $t = T_0$, where equation (5.4) ended.

In our future work we should investigate further the difficulties in the modelling of the diode. It might be convenient to use a Heavyside function in order to model the two states of this component.

The inertia of the system is modelled by an inductor. Consequently, the equations are not changed until after the flow has been reversed, that is until 2 ml. (F_{rev}) has run back. This means that equations (5.4) and (5.5) demand that $Q_A\,t > F_{rev}$ and $Q_A\,t \leq F_{rev}$, respectively. This can be compared with the physiological fact that the valve does not close before a certain amount of blood has passed backwards through the valve ([13, page 7]).

5.1.3 Equation three – compliance of the radial artery

Equation three deals with the compliance of the radial artery. The flow through this is obtained according to Kirchoff's current law. Hence, the flow through the compartment (Q_{RA}, the radial artery) is given by the flow entering the artery minus the flow present at the end of the artery (in the radial artery system) $Q_{RA} - Q_{RAS}$. The latter term is defined according to Ohm's law by P_{RA}/R_{RAS}, where R_{RAS} is the resistance of the arm. This is indicated by use of the subscript RAS. The resulting flow through the compliance is defined according to the definition given in figure 2.1 of chapter 2.

These considerations can be expressed in the following equation

$$C_{RA}\frac{dP_{RA}}{dt} = Q_{RA} - \frac{P_{RA}}{R_{RAS}} \tag{5.6}$$

where the resistance R_{RAS} is constant. The subscript RA refers to the radial artery.

5.1.4 Equation four – inertia of the radial artery

This equation uses the pressure difference between the aorta and the radial artery to predict the inertia of the radial artery. From a relation similar to Kirchoff's voltage law, it is possible to calculate the pressure difference from the sum of the resistance and the inertia of the radial artery. Using the basic definitions given in chapter 2 we can express the inertia as

$$\begin{aligned} P_A - P_{RA} &= R_{RA}\,Q_{RA} + L_{RA}\frac{dQ_{RA}}{dt} \quad \Leftrightarrow \\ L_{RA}\frac{dQ_{RA}}{dt} &= P_A - P_{RA} - R_{RA}\,Q_{RA} \end{aligned} \tag{5.7}$$

where both the resistance R_{RA} and the inertia L_{RA} are constant.

5.1.5 Equation five – the aortic compliance

This equation is used in order to predict the change in pressure through the aorta and hence the aortic compliance. Since the diameter and, thus the flow speed of the arterioles is much smaller than those of the arteries, the component representing the inertia is not taken into account. Therefore the equation is derived from Ohm's law alone. The flow is given by the flow in the aorta minus the flow passing through the radial artery minus the flow passing through the component defining the compliance of the aorta. The latter is represented as in the definition given in chapter 2. This gives rise to the following equation

$$\begin{aligned} P_{AE} - P_{VC} &= R_{VC}\left(Q_A - Q_{RA} - C_A \frac{dP_{AE}}{dt}\right) \quad \Leftrightarrow \\ C_A \frac{dP_{AE}}{dt} &= Q_A - Q_{RA} - \frac{P_{AE} - P_{VC}}{R_{VC}} \end{aligned} \tag{5.8}$$

where the resistance of the caval vein R_{VC} is constant.

5.1.6 Equation six – compliance of the caval vein

This equation predicts the flow and consequently the compliance in the caval vein. The prediction of the flow is based on Kirchoff's current law which says that the flow through the conductor is given by the flow present immediately below the resistance in the caval vein minus the flow below the systemic resistance R_S.

Using the basic definitions from chapter 2 we get

$$C_{VC} \frac{dP_{VC}}{dt} = \frac{P_{VC} - P_{AE}}{R_{VC}} - \frac{P_{VC}}{R_S} \tag{5.9}$$

where the resistances R_S and R_{VC} are constant.

5.1.7 Equation seven – inertia in the aorta

This equation predicts the pressure difference in the aorta. The derivation is analogous to that of equation four. However, it is important to remember that the flow through the aorta is given by $Q_A - Q_{RA}$. Using

the definitions from chapter 2 again, we find that the aortic inertia is given by

$$\begin{aligned} P_A - P_{AE} &= R_A(Q_A - Q_{RA}) + L_A \frac{d(Q_A - Q_{RA})}{dt} \quad \Leftrightarrow \\ L_A \frac{Q_A}{dt} &= P_A - P_{AE} - R_A(Q_A - Q_{RA}) + L_A \frac{Q_{RA}}{dt} \end{aligned} \tag{5.10}$$

where the resistance R_A and the inertia L_A are constant.

5.2 Definition of the elastance

The time-varying elastance concept used to model the cardiac ventricles is defined as the reciprocal of the compliance and can be thought of as the stiffness of the ventricles. This definition is due to [17].

$$C_V(t) = \frac{1}{E(t)} = \frac{V_V(t) - V_D}{P(t)} \tag{5.11}$$

$V_V(t)$ is the volume of the ventricles, V_D is the volume at zero pressure, and $P(t)$ is the pressure of the left and right ventricles, respectively.

The shape of $E(t)$, according to [17] is assumed to be some kind of a waveform. This is shown in figure 5.2.

In the simulator the elastance is modelled as an exponential charge curve during the systole and an exponential discharge curve during the diastole

$$E(t) = \begin{cases} E_{max}\left(1 - e^{-\frac{t}{\tau_1}}\right) + E_{min} & t < T_e \\ (E_{max} - E_{min})e^{-\frac{t-T_e}{\tau_2}} + E_{min} & t \geq T_e \end{cases} \tag{5.12}$$

where E_{max} and E_{min} are the maximal and minimal elastance of the ventricle in question[1], T_e is the time at the end of the systole, and τ_1 and τ_2 are the charge and the discharge times. In order to obtain continuity at $t = T_e$, τ_1 must be defined by

$$\tau_1 = \frac{T_e}{\log\left(\frac{E_{max}}{E_{min}}\right)}$$

[1]The maximal and minimal elastance are defined, respectively as E_{max_l}, E_{min_l} for the left ventricle and E_{max_r}, E_{min_r} right.

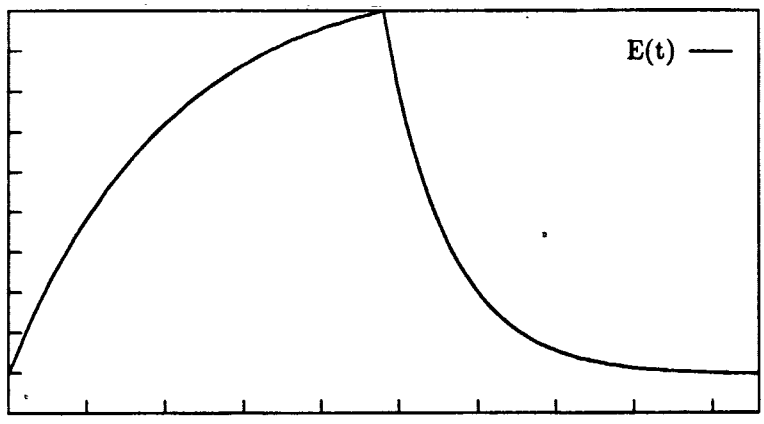


Figure 5.2: The elastance of the systemic circuit ($mmHg/ml$) shown as a function of time (s). The actual parameter values are described in appendix A

The discharge constant, equal to 0.4, allows us to define τ_2 in terms of τ_1: $\tau_2 = 0.4\,\tau_1$.

The minimum ventricular elastance used in (5.12) is determined by the end-diastolic ventricular pressure[2] P_{ED}.

$$E_{min} = \frac{P_{ED}}{V_{max} - V_D} \tag{5.13}$$

where V_D is the volume at zero pressure and V_{max} is the maximal ventricular volume, which is defined as:

$$V_{max} = 45.5 \log_{10}\left(\frac{P_{ED}}{0.48}\right)$$

The above definition has a variant for both the left and right ventricles.

The parameter E_{max} is empirically estimated to be 2.0 mmHg/ml in the systemic circuit, and 0.4 mmHg/ml in the pulmonary circuit (see next section).

[2] P_{ED} corresponds to the pressure of the caval vein P_{VC} or the pulmonary veins P_{PV} as predicted in sections 5.1 and 5.3.

The above equations should all be used on both the left and right ventricles. We will therefore refer to E_{max_l}, E_{min_l}, V_{DLV}, V_{DRV}, V_{max_l}, V_{max_r} as well as E_{max_r}, E_{min_r} in the following.

5.3 The models concerning the pulmonary circuit

These models are defined analogously with those of the systemic circuit. The only differences are the scaling of parameters and the natural lack of the upper extremity vasculature. The latter means that there are no equations similar to (5.6) and (5.7). Therefore the total number of equations modelling the pulmonary system is five.

The equations derived for the pulmonary models are obtained according to the circuit in figure 5.3.

5.3.1 Equation one – the right ventricle pressure

This equation is defined like equation (5.3) for the systemic circuit.

$$C_{RV}\frac{dP_{RV}}{dt} = -Q_{PA} - P_{RV}\frac{dC_{RV}}{dt} \tag{5.14}$$

5.3.2 Equation two – the pulmonary valve

This equation is derived exactly like the equations (5.4) and (5.5). The demand for the flow back into the ventricle is also present in this case.

$$\frac{dP_{PA}}{dt} = \frac{dP_{RV}}{dt} - R_{PV}\frac{dQ_{PA}}{dt} \qquad t\,Q_{PA} > F_{rev} \tag{5.15}$$

$$P_{PA} = P_{PAE} \qquad t\,Q_{PA} \leq F_{rev} \tag{5.16}$$

5.3.3 Equation three – compliance of the pulmonary artery

This equation is derived analogously to (5.8) except for the term representing the flow leaving the systemic circuit for the radial artery. Therefore:

$$C_{PA}\frac{dP_{PAE}}{dt} = Q_{PA} - \frac{P_{PAE} - P_{PV}}{R_{PV}} \tag{5.17}$$

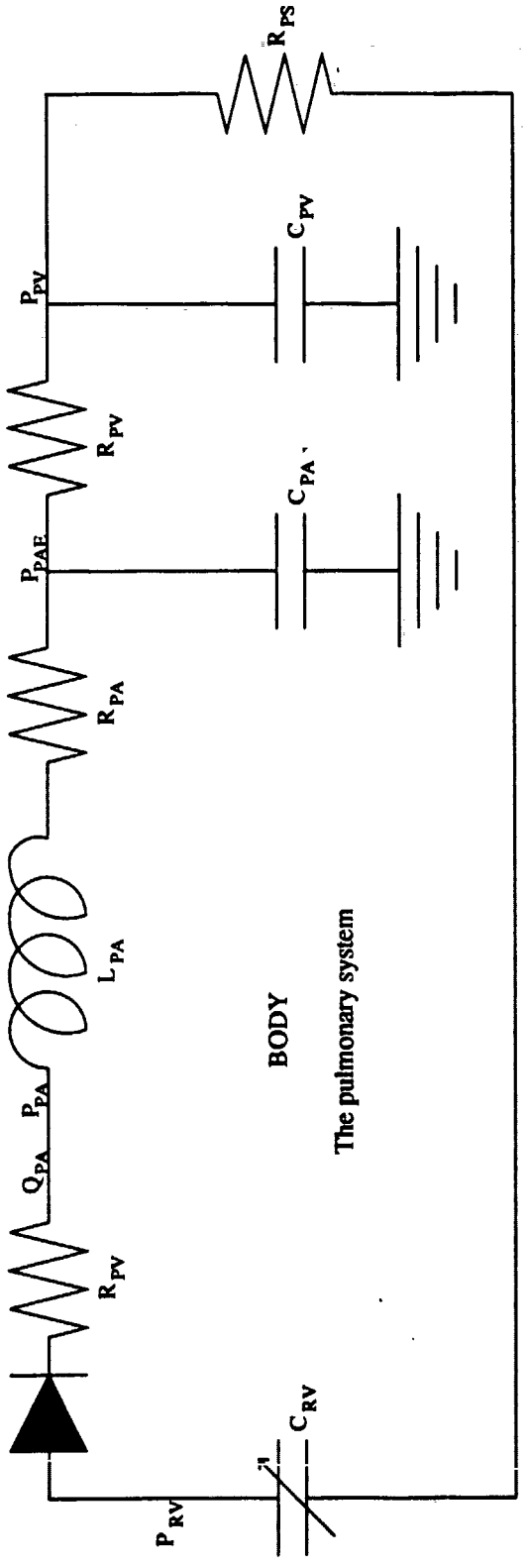


Figure 5.3: The pulmonary circuit.

5.3.4 Equation four – compliance of the pulmonary veins

This equation is defined exactly like (5.9). Therefore:

$$C_{PV}\frac{dP_{PV}}{dt} = \frac{P_{PV} - P_{PAE}}{R_{PV}} - \frac{P_{PV}}{R_{PS}} \tag{5.18}$$

5.3.5 Equation five – inertia of the pulmonary artery

The equation is derived analogously to (5.10) except that the flow in this case is Q_{PA}, since no blood has left the system.

$$L_{PA}\frac{Q_{PA}}{dt} = P_{PA} - P_{PAE} - R_{PA}\,Q_{PA} \tag{5.19}$$

5.4 Interaction between the systemic and pulmonary circuits

The two circuits are modelled separately, as described in sections 5.1 and 5.3. The only parameters exchanged between the models are the initial pressures at the entrance of the left and right ventricula, respectively. This is done once for every cardiac cycle. That is, the parameter containing the pressure in the caval vein P_{VC} is given as input to the right atrium, where the pressure is increased by δP_{RA} to the initial pressure P_{RV} in the pulmonary system. Analogously, the pressure predicted in the pulmonary vein P_{PV}, is transferred as an input to the left atrium.

The two models are linked by adding a right and left atrium as shown in figure 5.4.

In the models governing the systemic circuit the final pressure is the pressure of the caval vein. In the right atrium this pressure is raised by δP_{RATR} before it enters the right ventricle. The pressure increase in the left ventricle is made analogously by adding a pressure increment δP_{LA} to the pressure of the pulmonary veins. This way of modelling the pressure increase in the atria is quite simplistic and should probably be developed in further detail. Furthermore, it would be better if the two circuits were represented by one integrated model.

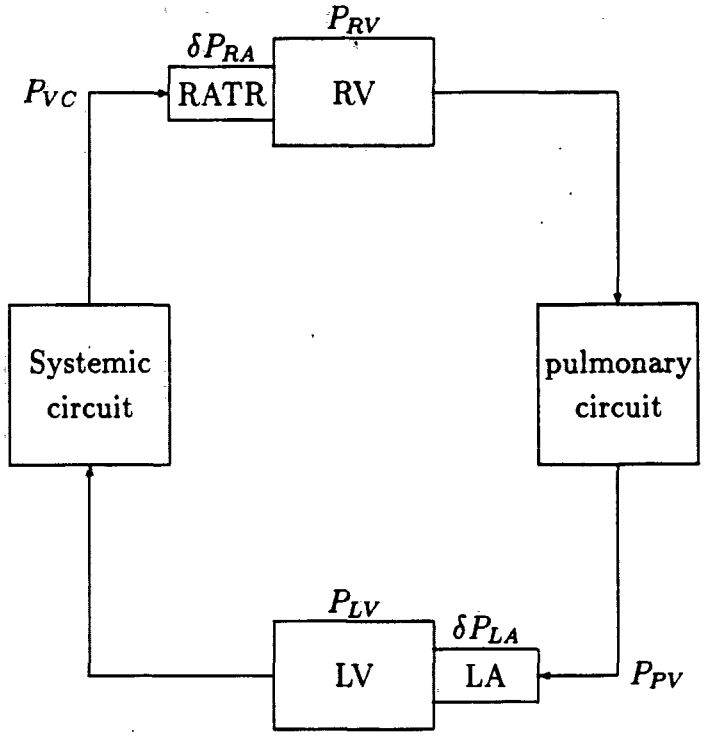


Figure 5.4: The linking of the two circuits and the relevant pressures governing the exchange of parameters. The abbreviations in the figure are defined as LV = Left Ventriculum, LA = Left Atrium, RV = Right Ventriculum and RATR = Right Atrium.

The linking equations for each cardiac cycle are due to the above considerations:

$$\begin{aligned} P_{LV} &= P_{PV} + \delta P_{RATR} \\ P_{RV} &= P_{VC} + \delta P_{LA} \end{aligned}$$

Chapter 6

The baroreceptor model

This model controls the pressure in the aorta, and it is mainly based on [11]. The output from this model is a change in the contractibility and, the pulse of the heart.

The mechanism that controls the aortic pressure of the cardiovascular system is called the baroreceptor. It is a result of a feedback control acting through the central nervous system. This control is obtained by the baroreceptor that converts the pressure in the carotid arteries to nerve signals. Studies of the baroreceptor control system [11, page 109] have shown, that the signals returned to the heart tend to regulate both the heart rate and the strength of contraction, in response to the pressure in the carotid arteries. Increased pressure entails a reduction of these, while decreased pressure has the opposite effect. Further, the baroreceptor has an effect on the peripheral resistance; however, this is not taken into account in our model.

Apart from the neural effects there is also a hormonal effect of the baroreceptor, resulting in the hormones adrenaline and noradrenaline being secreted from the medulla of the suprarenal gland. These secretions should therefore cause an input to the pharmacokinetical and pharmacodynamical models and therefore also in the cardiovascular model. However, this part of the baroreceptor has also been disregarded in our model.

Thus, this model only reflects the change in contractibility of the ventricles and the change in the heart rhythm as a function of the blood pressure. From this point of view the aortic pressure is the controlled variable, and the heart rate and the maximum elastance are the regulating parameters.

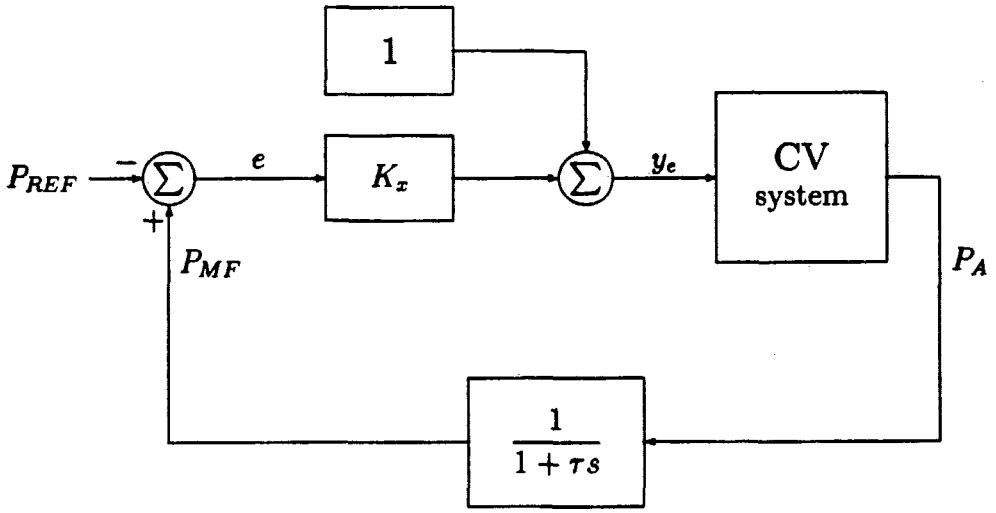


Figure 6.1: The regulation scheme representing the baroreceptor control. P_{REF} is the desired reference pressure and e is the difference between the reference and the mean pressure (i.e. the deviation). K_x is the factor used to regulate the deviation, which in turn determines the feedback quantity y_e. The latter is the control signal used to regulate both the heart rate and the maximum elastance of the heart.

The resulting contractibility is modelled by changing the parameters representing the maximal elastance of the left and right ventricles, respectively. (Further description of the elastance is given in section 5.2). The heart rhythm is simply modelled by changing the parameter for the basic heart rhythm.

The above regulation mechanism is illustrated in figure 6.1.

The feedback is accomplished according to the transducer function $\frac{1}{1+\tau s}$ given by [11, page 110]. The point is that the aortic pressure, which is a waveform, is smoothed so that we get a function for the mean pressure P_{MF} that can be regulated directly. The relation between the Laplace transformed mean pressure and the corresponding pressure in the aorta is given by

$$P_{MF}(s)(1+\tau s) = P_A(s) \tag{6.1}$$

in which we make use of results from the theory of Laplace transforma-

tions [9, page 382].

$$\begin{aligned}\mathcal{L}\{f'(t)\} &= \int_0^\infty f'(t)\,e^{-st}\,dt \\ &= f(t)\,e^{-st}\Big|_0^\infty + s\int_0^\infty f(t)\,e^{-st}\,dt \\ &= -f(0) + s\,\mathcal{L}\{f(t)\}\end{aligned}$$

Equation (6.1) can be transformed to

$$\frac{dP_{MF}}{dt} = \frac{1}{\tau}\,(P_A - P_{MF})$$

under the assumption that $P_{MF}(0) = 0$.

The feedback quantity is defined by

$$y_e = 1 + K_x\,(P_{MF} - P_{REF})$$

since only a proportional regulation factor (K_x) is used. If one needs a faster regulation one should also use an integration or even a differentiating factor. This way of defining both y_e and K_x is taken from [11]. When the mean pressure equals the reference pressure, no regulation is performed because $y_e = 1$.

Since the wavelength of the pulsewave is given by $\frac{1}{T}$, the pulse can be regulated by

$$HR^{reg} = \frac{1}{T_e + (T - T_e)\,y_e} \tag{6.2}$$

where HR is the heart rate, and the systemic period T_e is defined by $T_e = 0.14 + 0.2\,T$ (sec), in accordance with [11, page 110]. Furthermore, the regulated heart rate is given by $HR^{reg} = 20 + 60\,y_e$ (msec). We have assumed that the latter expression is given as stated in the denominator of equation (6.2). Similarly one can compute the regulated maximum elastance in the left and the right ventricle by:

$$E_{max}^{reg} = E_{max}\,\frac{2}{1 + y_e} \tag{6.3}$$

It would perhaps be obvious to define the regulated elastance by $\frac{1}{y_e}$. However, this could cause problems if y_e is close to zero. In our program

we limit the feedback quantity to 0.2, but even this value might cause numerical instability.

A common feature in equations (6.2) and (6.3) is that if the pressure in the aorta equals the reference pressure, then no regulation takes place and both variables will keep their original values.

As stated in the introduction to this chapter, this definition of the barorecepter is not adequate. One should therefore invest more time in order to get a better model for the baroreceptor.

Chapter 7

Input and output from the models

The simulator is based on a total of six models. They interact as displayed in figure 7.1.

The input parameters come either from the basic constant values mentioned in appendix A or are taken from the actual case. In the latter situation a user-defined script includes these basic parameters. However, if the script is disabled, the input parameters are prescribed interactively by the user.

All output parameters are sent to the anaesthetic equipment through the interface described in chapter 8. This includes some transformation of the given binary signals in order to get the right information on the anaesthetic monitors.

The input, output and exchange of parameters is done for every heart cycle, and the following description therefore only concerns one heart cycle.

7.1 The cardiovascular model

The cardiovascular model consists of two parts, one for the systemic and one for the pulmonary circuit. When running a simulation one can display the various pressures from either the systemic or the pulmonary part. However, both models are running at all times in order to get the right interaction.

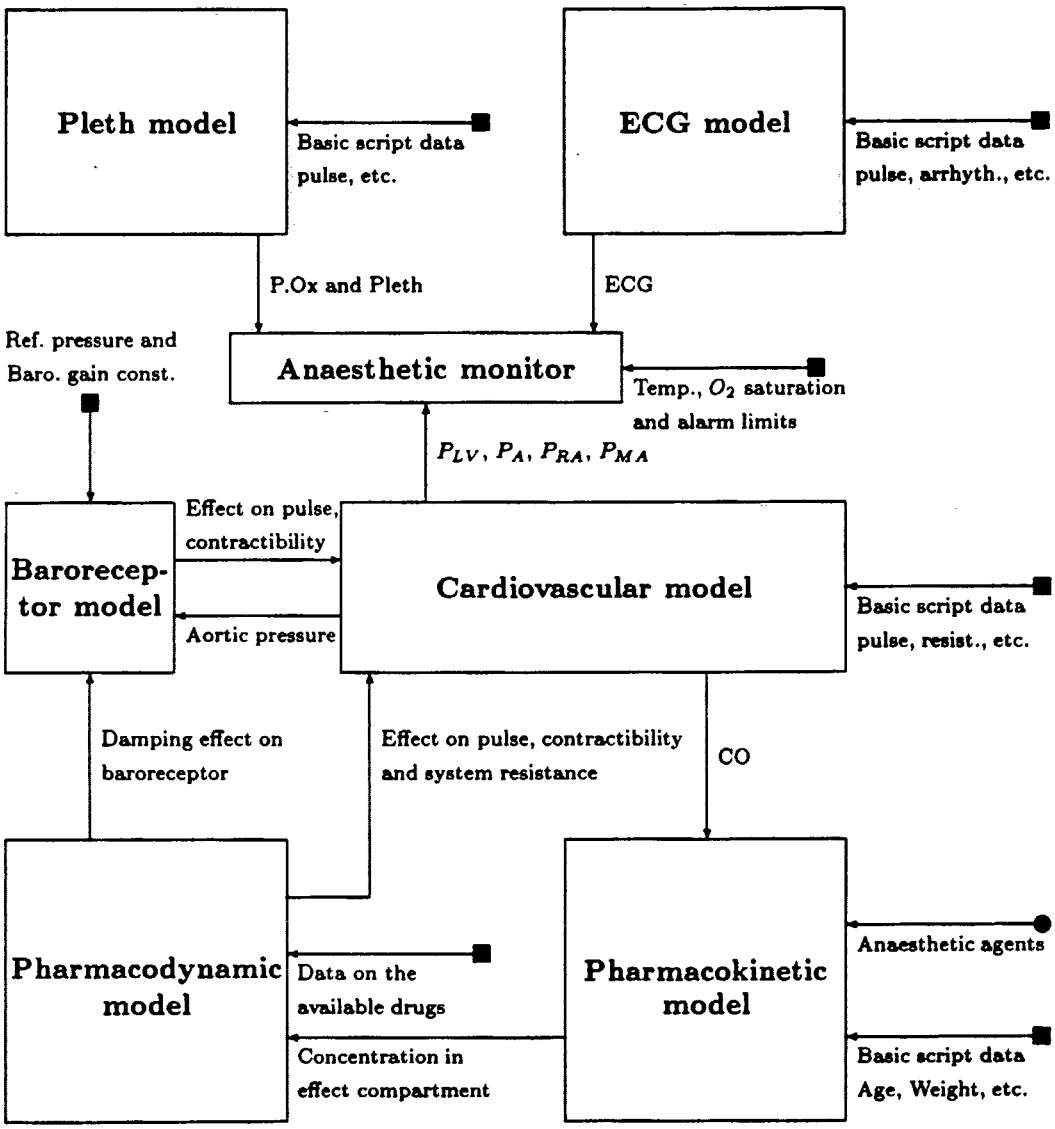


Figure 7.1: The model dependencies.

The model is predicts the cardiac output and the pressures in the aorta, radial artery, pulmonary artery and venous system as well as the mean aortic pressure. The latter is calculated by filtering the aortic pressure. Furthermore, the cardiac output is transferred as a parameter to the pharmacokinetic model.

7.1.1 Input parameters

The systemic circuit	
HR	Heart rate $[beat/min]$
E_{max_l}	Left ventricle max elastance $[mmHg/ml]$
R_{AV}	Resistance aortic valve $[mmHg\,s/ml]$
R_A	Resistance aorta $[mmHg\,s/ml]$
R_{VC}	Resistance caval vein $[mmHg\,s/ml]$
R_S	Resistance systemic aortic system $[mmHg\,s/ml]$
R_{RA}	Resistance radial artery $[mmHg\,s/ml]$
R_{RAS}	Resistance radial artery system $[mmHg\,s/ml]$
L_A	Inductance aorta $[mmHg\,s^2/ml]$
L_{RA}	Inductance radial artery $[mmHg\,s^2/ml]$
C_A	Compliance aorta $[mmHg/ml]$
C_{VC}	Compliance caval vein $[mmHg/ml]$
C_{RA}	Compliance radial artery $[mmHg/ml]$
V_{DLV}	Volume (dead) left ventricle $[ml]$
δP_{LA}	Pressure incr left atrium $[mmHg]$
P_{A0}	Initial aortic pressure $[mmHg]$
T_e	End ejection time $[s^-1]$
F_{rev}	Aortic and pulm reverse flow $[ml]$

The pulmonary circuit	
HR	Heart rate $[beat/min]$
E_{max_r}	Right ventricle max elastance $[mmHg/ml]$
R_{PV}	Resistance pulm valve $[mmHg\,s/ml]$
R_{PA}	Resistance pulm artery $[mmHg\,s/ml]$
R_{PV}	Resistance pulm veins $[mmHg\,s/ml]$
R_{PS}	Resistance pulm artery system $[mmHg\,s/ml]$
L_{PA}	Inductance pulm artery $[mmHg\,s^2/ml]$
C_{PA}	Compliance pulm artery $[mmHg/ml]$
C_{PV}	Compliance pulm veins $[mmHg/ml]$
V_{DRV}	Volume (dead) right ventricle $[ml]$
δP_{RA}	Pressure incr right atrium $[ml]$
P_{P0}	Initial pulm artery pressure $[mmHg]$
T_e	End ejection time $[s^-1]$
F_{rev}	Aortic and pulm reverse flow $[ml]$

7.1.2 Output parameters

The systemic circuit	
P_{LV}	Pressure left ventricle $[mmHg]$
P_A	Pressure aorta $[mmHg]$
P_{MA}	Pressure mean aorta $[mmHg]$
P_{VC}	Pressure caval vein $[mmHg]$
P_{RA}	Pressure radial artery $[mmHg]$

The pulmonary circuit	
P_{RV}	Pressure right ventricle $[mmHg]$
P_{PA}	Pressure pulm artery $[mmHg]$
P_{MPA}	Pressure mean pulm artery $[mmHg]$
P_{PV}	Pressure pulm veins $[mmHg]$

7.1.3 Exchange of parameters

The cardiac output (Q_A respective Q_{PA}) is transferred to the pharmacokinetic model. Furthermore, the pressures from the caval (P_{VC}) and the pulmonary veins (P_{PV}) are passed as inputs to the right and left atria, respectively.[1] Finally the aortic pressure is passed to the baroreceptor model.

[1] For a detailed explanation see section 5.4.

7.2 The baroreceptor model

The baroreceptor model controls the pressure in the aorta. The output from this model is a change in the contractibility, pulse of the heart and resistance of the arteries.

7.2.1 Input parameters

P_{REF}	Baroreceptor pressure reference $[mmHg]$
K_x	Baroreceptor gain constant

7.2.2 Exchange of parameters

The effect of the baroreceptor is a regulation of the heart rhythm (HR), and a change of the maximal elastance of the left (E_{max_l}) and right (E_{max_r}) ventricles. These variables are transferred to the cardiovascular model once for every heart cycle. Furthermore, the pharmacodynamic model is changing the gain constant in order to damp the baroreceptor effect when the body is influenced by anaesthetics.

7.3 The pharmacokinetic model

The pharmacokinetic model consists of:

A fourteen-compartment model that describes the concentration of the inhalational agents in fourteen compartments of the body.

A three-compartment model that predicts the concentration of the injected drugs in the plasma and in fictive effector compartments.

7.3.1 Input parameters

The fourteen-compartment model	
PatWght	Patient body weight $[g]$
PatHght	Patient body height $[m]$
PatAge	Patient age [year]
Gender	woman [0], man [1]
Temp	Patient temperature $[C°]$
Fs	Pulmonary shunt fraction of cardiac output
Vc	Volume of anaesthetic circuit $[l]$

In the three-compartment model the following constants must be defined for all possible drugs.

The three-compartment model	
V_n	Volumes for the fictive compartments $[l]$
k_{ij}	The rate of flow from compartment i to compartment j $[m/s]$

7.3.2 Exchange of parameters

When using the fourteen-compartment model, the predicted concentration in the brain is transferred to the pharmacodynamic model. In case of the three-compartment model this transferred concentration belongs to a fictive compartment representing the plasma concentration. The only input from other models is the cardiac output, which is provided by the cardiovascular model.

7.4 The pharmacodynamic model

The pharmacodynamic model converts the concentration C of the agents in the effector compartment to clinical effects using the Hill equation (see page 20). This approach uses the hypothesis that drug effects are related to a number of occupied receptors mediating the clinical response. The clinical effects are transferred to the cardiovascular and the baroreceptor models.

7.4.1 Input parameters

For all possible drugs the following constants must be defined:

Ce_{50}	The effect compartment concentration resulting from a 50% effect dose
MaxE	The maximal effect on the heart rate, vascular resistances and maximal elastances

7.4.2 Exchange of parameters

The dynamic effect of the administered drugs is a damped baroreceptor gain constant and various effects of the heart rate (HR), the contractibility of left (E_{max_l}) and right (E_{max_r}) ventricles and the system resistance of the systemic (R_S) and pulmonary (R_{PS}) circuit.

7.5 The ECG model

The ECG model predicts the ECG wave continuously.

7.5.1 Input parameters

The input is the heart rhythm and one of the arrhythmias or extrasystoles, etc., defined in appendix A.

7.5.2 Output parameters

The model sends a smooth ECG wave to the anaesthetic monitor.

7.6 The plethysmographic model

The plethysmographic model predicts the pleth according to the strength of the pulse.

7.6.1 Input parameters

T_e	End ejection time $[s^{-1}]$
A	The amplitude of the pulse oximeter

7.6.2 Output parameters

A continuous curve predicting the pleth.

7.7 From user scripts

Some of the parameters transferred to the anaesthetic equipment come from global constants either stated directly in the user scripts, prescribed interactively during a simulation or are taken as the default values mentioned in appendix A. That is:

Sat	Pulse oximeter oxygen saturation
losat	Pulse oximeter low saturation alarm limit
hisat	Pulse oximeter high saturation alarm limit
lorate	Low pulse rate alarm limit [beat/min]
hirate	High pulse rate alarm limit [beat/min]
Temp	Patient temperature [$C°$]

Chapter 8

The interface

The data for the anaesthetic monitors are sent from the PC through the serial port and through a D/A converter connected to the ISA bus. The former is used for numerical variables such as temperature or pleth, while the latter is used for the waveforms describing ECG and the various pressures.

8.1 The waveforms

The D/A converter has 16 ports enumerated from 0 to 15. Each waveform is assigned to a port as shown in the following table:

1. ECG – the filtered wave as described in the section about the ECG-model.

3. P_{MA} – the mean aortic pressure. This is calculated as an average of the aortic pressure obtained from the cardiovascular model.

5. Plethysmograph – the sine curves displaying the quality of the received signal from the pulseoximeter probe.

6. Temperature – there is no models for predicting the temperature. It is taken from the userdefined scripts and passed directly as output.

9. P_{LV} – the left ventricular pressure as predicted in the cardiovascular model.

10. P_A – the invasive aortic pressure as predicted in the cardiovascular model.

11. P_{VS} – the venous system pressure as predicted in the cardiovascular model.

15. P_{RA} – the invasive radial artery blood pressure is predicted in the cardiovascular model.

8.2 The numerical data

The numerical data are encoded into a string of 45 characters and are periodically transmitted through the serial port.

The string starts with the special character <STX> (ASCII - 002) followed by 43 data characters and it is closed with a <CR> (ASCII 013). The format of the data characters is

$$RnnnSnnnPnnnLnnnHnnnOnnnAnnnMnnnTnnnnnnQnnn$$

where n is a decimal digit and the identifiers are given as follows:

R: Pulse frequency
S: Saturation (Oxygen) % – taken directly from the script
P: Pulse amplitude
L: Low rate alarm limit (default=030)
H: High rate alarm limit (default=200)
O: Low saturation alarm limit (default=070)
A: Alarm status
M: Monitor status
T: Time
Q: High saturation alarm limit (default=100)

The parameters S, P, and the the alarm limits are taken directly from the script.

Chapter 9

The course of a simulation

The point of departure in any simulation is a scenario, which is constructed by transforming a case from the operating theater into the input needed by the simulator. The input consists of basic patient data such as bodyweight, height etc. as well as a sequence of events planned to happen at some predefined times during the simulation. These data are written into a script file consisting of a number of lines each defining a given change of a certain model parameter.

The script thus generates the various incidents or catastrophes that might happen during anaesthesia. The use of scripts facilitates the running of the scenarios and ensures uniform progress of the incident at each repetition. The script language contains two alternative modes, either an absolute mode where the parameters are assigned a new value or a relative mode where the current values are modified by the script statement. The two modes are freely interchangeable in the scripts. The absolute mode ensures the possibility for standardization of the excesses during the incidents. This secures that the scenarios can be analysed and compared later for scientific purposes.

The syntax of a script is:

```
PARAMETER

  <hh:mm:ss>    <name>      <relative change of parameter>
  <hh:mm:ss>    <name>  =   <absolute change of parameter>
  ...
  ...
END
```

9.1 Cardiac arrest – an example of a scenario

From a clinical point of view cardiac arrest is a condition where both quick and adequate measures ensuring ventilation and circulation have to be taken, but also diagnosis of causes and differential diagnoses are important in order to reveal disconnects of hoses, etc.

Treatment of cardiac arrest has been discussed intensely over the years and the recommended procedures are taught to physicians frequently. These procedures are, however, quite complex and are often inadequate due to specific conditions in the patient. The possibilities for training and acquiring experience in management of the whole anaesthetic crew are limited. Cardiac arrest is therefore a typical example of the use of the simulator.

9.1.1 The scenario given to the trainee

In the cardiac arrest case the following scenario is presented to the trainee:

> **The Patient:** *The patient is a forty-three-year old male from Greenland who must undergo a fundoplicatio for a symptomatic hiatus hernia. During the past 15 years many endoscopies have consistently confirmed the diagnosis, including distal esophageal ulcerations due to regurgitation. The patient has had no benefit at all from conservative treatment. Never previously hospitalized. The clinical examination is completely normal.*
>
> **The anaesthesia:** *Crush induction, due to risk of regurgitation and subsequent aspiration to the lungs. Maintenance with isoflurane, fentanyl and vecuron.*

The paraclinical measures: *Hgb (8.5 mmol/l), creatinin (105 micromol/l), Na (145 mmol/l), K (3.5 mmol/l) and urine stix are normal. Six portions of blood (500 ml each) available. Completely straightforward!*

The situation: *You are taking over immediately after induction, since the anaesthetist in charge has been permitted to leave.*

This is all the information the subject gets! The further development of the scenario is kept secret from the subject.

9.1.2 Description of the intended course of the scenario

The first seven minutes are quiet despite some occasions with ectopics of no significance. Then the surgeon asks the subject to insert a gastric tube. Fibrillation starts when the subject is occupied with insertion of the gastric tube. This will immediately turn on most of the alarms on the monitors. The subject is supposed to recognize that cardiac arrest is occurring and discover the absence of the pulse. In this case the subject must immediately stop administration of anaesthetics, turn on 100% oxygen, and start chest compressions. This must be continued until a defibrillator is available, whereafter the patient is defibrillated with 200 joules. If there is no effect, as is the case in this scenario, two further defibrillations and the administration of lignocaine are necessary. After two minutes the patient will, according to the script, develop asystolia, and now adrenaline is indicated as well. The final outcome depends on the performance of the trainee.

This story is transformed into the following script:

```
/* script.dat */
/* Cardiac arrest */

PARAMETERS                  ; Comments
0:05    BaseHr    = 95      ; start conditions,
                              (=) means absolute
                              mode
0:10    XSys      VES       ; start conditions:
                              Occasional ectopics
0:10    Freq      Occ       ; start conditions
```

```
3:01    XSys      NoArr     ; Stop of ectopics
3:05    RVEmax     0.01     ; Increased heart pumping,
                              no (=) means relative mode.
3:06    LVEmax     0.5
3:07    BaseHr    -3        ; Decreasing heart rater
3:35    BaseHr    -4
4:05    Sat       -3        ; Decreasing oxygen
                              saturation
5:55    BaseHr    -5
6:05    BaseHr    -3
6:15    BaseHr    -4
6:30    BaseHr    -4
6:30    XSys      VES       ; Start again of ventricular
                              ectopics
6:30    Freq      Occ
7:05    Arr       VF        ; Assystolia starts:
9:05    Arr       Asys      ; Cardiac arrest with
                              ventricular fibrillation
END

FINISH
```

There are no entries concerning the basic patient data, as the script above uses the default values described in appendix A.

Chapter 10

Model improvements

The models contained in the simulator today are far from comprehensive. In this chapter we will therefore try to clarify the project status.

We will discuss the status, point out the problems and if possible we will suggest fields of future efforts. This will be done for all six models.

10.1 The pharmacokinetic and dynamic models

The pharmacokinetic model is currently divided in two, a fourteen-compartment model predicting the concentration of the inhalational agents and a three-compartment model predicting the concentration of the intravenous agents.

The first model is very elaborate because it explicitly calculates the concentration in all fourteen compartments, and this is not necessary in the present simulator, since only the brain concentration is used in order to predict the effect.

On the other hand, since all compartments are modelled separately, a future version of the simulator could incorporate the effect of drug distribution during conditions with great deviations in regional blood flows. An example of this is the difference in bloodflows under either parasympathic or sympathic stress, where the fine-grained fourteen-compartment model could be exploited better.

The three-compartment model, however, is too simplistic and it has the disadvantage of not being based on a physiological theory. A group

of students at Roskilde University Centre is currently working on a physiological multiple-compartment model for a few intravenous agents. Their work might be useful in order to establish a general physiological model for intravenous agents as such.

Today the simulator is limited to about eighty of the most commonly used drugs in Denmark. To adapt to practices in other countries, the simulator should be extended with the medications available in those countries.

10.2 The ECG model

The concept of letting the ECG be generated by filtering various step functions is good. However, the simulator should contain more kinds of arrhythmias and the possibility to display the phenomenas happening when using the DC-defibrillator.

10.3 The cardiovascular model

We have identified three weaknesses in the current cardiovascular model.

First, the model is described through the use of electrical circuit analogs, and is too simple since it does not take the spatial dimensions into account. For instance the aorta is regarded as a system with no spatial extension. A consequence of this is that all changes happen simultaneously. Second, the representation of the valves is not adequate. Third, the systemic and the pulmonary circuits are only loosely linked together.

An alternative is to model the cardiovascular system by using theory from fluid dynamics and thereby view the system in either one, two or three spatial dimensions.

In this sense one can model the aorta as combined of pieces each representing a part of the tube. In one of these one could model the aortic arch, and in some others one could model some of the major branches. Yet another piece could model an outflow for the remaining branches. Each piece could then be modelled in a fluid dynamical way, and the coupling between the pieces could be made through the boundary conditions.

Along with this approach one should model the ventricles, the aortic and pulmonary valve as well as the pulmonary circuit.

However, the use of more spatial dimensions does not necessarily provide more insight than does a one-dimensional approach. Furthermore, one must take the computational effort into account. This tends to be immense when higher dimensional systems are to be calculated. This could present a problem if the model is required to run on a personal computer.

Even if it appears to be impossible to employ the fluid dynamic approach in a realtime simulator, the development could still provide insight as well as ideas to make the best possible zero-dimensional approach.

10.4 The baroreceptor model

The baroreceptor is modelled as a feedback system, where the theory of [11] is used. However it takes neither the changes in the peripheral resistance nor the humeral effects into account.

10.5 Miscellaneous models

In general, one should make the temperature dependent on the other model parameters instead of letting it be a constant.

Concerning the design of the program, a more general graphical user interface (GUI-based) approach would be more appropriate.

Furthermore, the following minor problems should be addressed:

- It should be possible to run more simulations at a time without leaving the program. This calls for the possibility to choose another case and thereby reset all parameters according to the case in question.
- It should be possible to access more windows at any given time.
- It should be possible to control the mechanical CO_2 device from the computer.

- It should be possible to make breathing sounds in order to make it easier to stethoscope the mannequin. This can easily be done by inserting additional speakers in the chest of the mannequin, and it is currently being addressed.

The addition of all these concepts could be very complicated indeed if everything is to be run on one computer. However, the important goal is that control is maintained from one terminal. The program itself could, in fact, be distributed on several computers.

The above mentioned problems are of varying importance. The main task is to redesign the cardiovascular model and to make sure that the pharmacokinetic and ECG models are working correctly. The problems concerning the design and building in the CO_2 are for the moment less essential.

Appendix A

The system constants

Most of the parameters, especially for the cardiovascular and the pharmacodynamic models, are taken from [14].

In the description of the models throughout this report various constants have been used. This appendix therefore contains the actual values for all these constants. They are grouped according to the model which they belong to.

A.1 The ECG arrhythmias

The exact definition of these arrhythmias is displayed in tables of 60 equidistant numbers.

Here we will only display the possible arrhythmias.

The basic arrhythmias	
SR	Sinus rhythm (regular)
ST_1	ST depression 1 mm
ST_2	ST depression 2 mm
ST_3	ST depression 3 mm
ST_5	ST depression 5 mm
VT	Ventricular Tachycardia
AF	Atrial Febrillation
VF	Ventricular Febrillation
Asys	Asystole

Possible extrasystolia	
NoArr	No Arrhythmia
SVES	Supraventricular extrasystoles
$SVES_2$	Run of two SVES
VES	Ventricular extrasystoles
VES_2	Run of two VES
VES_3	Run of three VES

Possible frequency of extrasystoles	
Big	Bigeminy
Tri	Trigeminy
Tetra	Tetrageminy
Occ	Occasional

A.2 The plethysmographic model

The only constants used in this model are the period T_P and the half period T_0 of a heart cycle. They are both seen as fractions of seconds $[s^{-1}]$.

T_e	0.24	End injection time (a quarter period) $[s^{-1}]$
T_P	$4\,T_e$	The period of a heart cycle $[s^{-1}]$
T_0	$2\,T_e$	The half period of a heart cycle $[s^{-1}]$
A	100	The amplitude of the pleth

A.3 The pharmacokinetic and dynamic models

PatWght	52.0e3	Patient body weight $[g]$
PatHght	1.80	Patient body height $[m]$
PatAge	40	Patient age [year]
Gender	1	woman [0], man [1]
Temp	37.00	Patient temperature $[C°]$
Fs	0.005	Pulmonary shunt fraction of cardiac output
Vc	6.50	Volume of anaesthetic circuit $[l]$

For all available drugs the following are needed:

In case of the three-compartment model, all the volumes V_n of the fictive compartments and the flow rate k_{ij} from compartment i to compartment j.

For the pharmacodynamical model, the values of the maximal effect on the various parameters mentioned in chapter 7. Furthermore, the 50% effect and the class effects should be known. The concrete information on these topics can be found in [10].

A.4 Interface

The default values of the parameters sent directly from the userscript to the anaesthetic equipment are given as:

A	100.00	Pulse oximeter pulse amplitude
Sat	95.00	Pulse oximeter oxygen saturation
losat	70.00	Pulse oximeter low saturation alarm limit
hisat	100.00	Pulse oximeter high saturation alarm limit
lorate	30.00	Low pulse rate alarm limit [beat/min]
hirate	200.00	High pulse rate alarm limit [beat/min]

A.5 The cardiovascular and the baroreceptor models

HR	68	Heart rate $[beat/min]$
E_{max_l}	2.00	Left ventricle max elastance $[mmHg/ml]$
E_{max_r}	0.40	Right ventricle max elastance $[mmHg/ml]$
R_{AV}	0.002	Resistance aortic valve $[mmHg\,s/ml]$
R_A	0.06	Resistance aorta $[mmHg\,s/ml]$
R_{DA}	0.02	Resistance distal aorta $[mmHg\,s/ml]$
R_S	0.80	Resistance systemic aortic system $[mmHg\,s/ml]$
R_{RA}	1.20	Resistance radial artery $[mmHg\,s/ml]$
R_{RAS}	50.00	Resistance radial artery system $[mmHg\,s/ml]$
R_{PV}	0.002	Resistance pulm valve $[mmHg\,s/ml]$
R_{PA}	0.06	Resistance pulm artery $[mmHg\,s/ml]$
R_{PDA}	0.10	Resistance pulm distal artery $[mmHg\,s/ml]$
R_{PS}	0.10	Resistance pulm artery system $[mmHg\,s/ml]$
L_A	$5.0e-4$	Inductance aorta $[mmHg\,s^2/ml]$
L_{RA}	0.10	Inductance radial artery $[mmHg\,s^2/ml]$
L_{PA}	$5.0e-4$	Inductance pulm artery $[mmHg\,s^2/ml]$
C_A	2.00	Compliance aorta $[mmHg/ml]$
C_{DA}	100.00	Compliance distal aorta $[mmHg/ml]$
C_{RA}	0.02	Compliance radial artery $[mmHg/ml]$
C_{PA}	7.00	Compliance pulm artery $[mmHg/ml]$
C_{PDA}	50.00	Compliance pulm distal artery $[mmHg/ml]$
V_{DLV}	13.50	Volume (dead) left ventricle $[ml]$
V_{DRV}	10.00	Volume (dead) right ventricle $[ml]$
δP_{LA}	5.00	Pressure incr left atrium $[mmHg]$
δP_{RA}	2.00	Pressure incr right atrium $[ml]$
P_{A0}	80.00	Initial aortic pressure $[mmHg]$
P_{P0}	10.00	Initial pulm artery pressure $[mmHg]$
T_e	0.24	End ejection time $[s^-1]$
F_{rev}	2.00	Aortic and pulm reverse flow $[ml]$
P_{REF}	80.00	Baroreceptor pressure reference $[mmHg]$
K_x	0.02	Baroreceptor gain constant

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